



Dynamic myelin regulation as a novel form of neural plasticity

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ABSTRACT

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Dynamic changes in myelin could optimize information transmission in neural circuits and enhance conduction velocity. This review aimed to provide an understanding of how dynamic myelin plasticity is important in neuronal activity and how astrocytes have an important role that is not equal in the peripheral nervous system. Myelin is dynamically regulated by neuronal activity. It takes part continuously in nervous system plasticity during development. Newly differentiating oligodendrocytes can create a new myelin sheath. Mature myelin sheaths can grow again in adults. Oligodendrocytes interact with astrocytes in the central nervous system through gap junctions. Astrocytes have an important role as synaptic network integrators; therefore, decreasing astrocyte numbers will cause a loss of presynaptic plasticity. The concept considers plasticity as a mechanism that depends on myelination. Higher brain functions and myelination interplay in the hippocampus and prefrontal cortex. The mechanism and function of these changes remain poorly understood. Genetic, neural activity, environment, and axonal activity might play important roles. Dynamic myelin regulation reveals a new form of neural plasticity. Myelination is similar to synapse formation and plasticity. It enables plasticity in the central nervous system and helps improve the learning process.

ABSTRAK

Perubahan dinamis pada mielin dapat mengoptimalkan transmisi informasi dalam sirkuit saraf dan meningkatkan kecepatan konduksi. Ulasan ini bertujuan untuk memberikan pemahaman tentang betapa dinamika plastisitas mielin adalah penting dalam aktivitas neuron dan bagaimana astrosit memiliki peran penting yang tidak ada bandingannya dalam sistem saraf tepi. Mielin diatur secara dinamis oleh aktivitas neuron. Mielin berperan terus menerus dalam plastisitas sistem saraf selama perkembangan. Oligodendrosit yang baru dapat membuat selubung mielin baru. Selubung mielin dewasa dapat tumbuh kembali pada orang dewasa. Oligodendrosit berinteraksi dengan astrosit di sistem saraf pusat melalui persimpangan gap. Astrosit berperan penting sebagai integrator jaringan sinaptik, oleh karena itu, penurunan angka astrosit akan menyebabkan hilangnya plastisitas presinaptik. Konsep ini mempertimbangkan plastisitas sebagai mekanisme yang tergantung pada mielinisasi. Fungsi otak yang lebih tinggi dan mielinisasi saling berinteraksi di hipokampus dan korteks prefrontal. Mekanisme dan fungsi perubahan ini masih belum dipahami sepenuhnya. Faktor genetik, aktivitas saraf, lingkungan, dan aktivitas aksonal kemungkinan berperan penting dalam perubahan tersebut. Regulasi mielin yang dinamis mengungkapkan bentuk baru dari plastisitas saraf. Mielinisasi mirip dengan pembentukan sinapsis dan plastisitas. Ini memungkinkan plastisitas di sistem saraf pusat dan membantu meningkatkan proses pembelajaran.

Keywords:

dynamic;
myelin;
plasticity;
neural;
astrocyte;

INTRODUCTION

Myelin is the multilaminar sheath on axons. It is formed in the central nervous system (CNS) by glial cells, namely, oligodendrocytes.¹ In the peripheral nervous system (PNS), the myelin sheath is formed by spindle-shaped Schwann cells. Myelination is important for saltatory conduction. Saltatory conduction is special because it requires less energy consumption, but it has a higher speed.²

Myelination in the CNS is an

on going process that starts around birth and continues throughout life. Some aspects of myelination can be modulated by extrinsic signals, including neuronal activity. Neuronal activity can regulate myelin formation through oligodendrocyte differentiation and myelination. Myelination should be maintained at an optimal level to assure normal central nervous system function, especially in the hippocampus and prefrontal cortex area. Otherwise, there are some disorders as described in FIGURE 1.^{2,3}

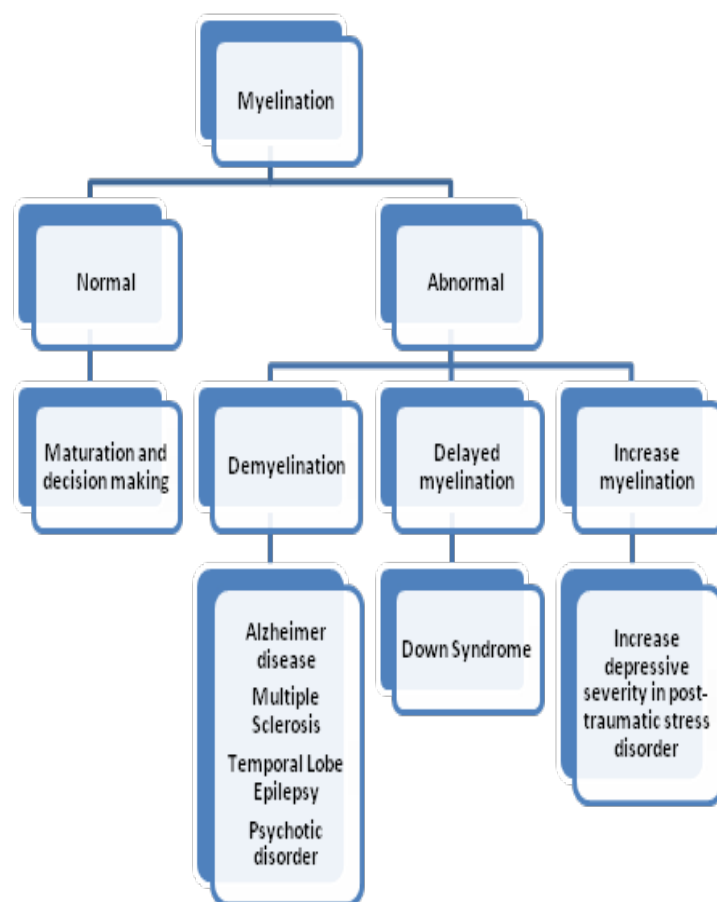


FIGURE 1. Myelination and its associated condition^{2,3}

Myelination in the peripheral nervous system involves morphological changes in Schwann cells, such as cellular process extension and retraction, membrane wrapping, ensheathment, and compaction. Cellular protrusions sort larger axons to be myelinated. The inner membrane is wrapped. Cell shapes

are changed according to rearrangement of the actin cytoskeleton.^{4,5}

Myelin, that rich in lipids, enables the thinner axon to transmit information more rapidly than an unmyelinated axon. Some axons are unmyelinated. For example, less than half of axons in the corpus callosum become myelinated.

Only axons with a diameter of more than 0.4 μm can be myelinated. Activity-dependent secretion stabilizes myelin sheath formation on selected axons.⁶ The abundance of myelinated axons in the central nervous system connective tracts will produce a whitish color on white matter. This will make up approximately half of the human brain volume.⁷

Myelination affects action potential conduction velocity. Activity-dependent myelination greatly impacts spike timing and Hebbian learning. Myelination of specific axons might be crucial for normal brain function. Therefore, some neuropsychiatric disorders have been linked to myelin genes and white matter abnormalities. Social isolation experiments from postnatal 21–35 days of mice revealed altered prefrontal cortex myelination. Experience and neuronal activity may change the behavior of myelinating oligodendrocytes. Altered experience can affect myelinogenic conditions.⁸

Myelin plasticity is important in complex information processing tasks that involve coupling and synchronizing among different brain rhythms. Disturbance in myelination might lead to dysfunction in the nervous systems, such as epilepsy, schizophrenia, or dyslexia.⁹ Plasticity is mediated through myelination. Myelination will modulate conduction velocity to reduce temporal delay.^{10,11} Myelin increases conduction velocity and supports nervous system plasticity.¹²

Myelin plasticity is a mechanism for modifying conduction delays to optimize rhythmic activity in the brain. The ability to produce such adaptive changes would distinguish between normal and abnormal nervous system function. Myelin plasticity is important in maintaining normal oscillatory brain activity. This mechanism of nervous system plasticity will produce stable interactions between different oscillators. Finally, this process will

enhance functional performance, learning, and overall dynamical stability.¹⁰

Regulation of myelination has been proposed as a form of nervous system plasticity. The reason is that the timing of communication between neurons affects synaptic plasticity ensembles with the functional properties of neurons. Comprehensive research and studies about myelination are essential because impaired myelin regulation is often related to learning and cognition deficits, as well as psychiatric disorders. Many imaging studies of white matter plasticity assume myelin change as a potential mechanism. Myelin is not merely passive electrical insulation but is going through dynamic development into early adulthood.⁸ Myelination of unmyelinated axons and modification of the myelin sheath are important in myelin remodeling.¹³⁻¹⁵ In another study, the thin myelin sheath was thicker with time until reaching normal thickness due to oligodendrocyte plasticity.¹⁶ Oligodendrocyte-astrocyte coupling occurs during axon metabolic support.¹⁷ Astrocytes might enhance plasticity because they have an important role in synapse and neurotransmitter regulation. More activated astrocytes involved in synaptic plasticity will yield higher expression of glial fibrillary acidic protein (GFAP).^{6,18} Astrocytes have intrinsic plasticity. It is an essential part of the cellular mechanism together with neurons and oligodendrocytes. These cells participate in injury recovery.¹⁹ The process is known as gliogenesis and neurogenesis.²⁰ Esen *et al.*⁹ found that astrocytes together with pericytes, endothelial cells, and neurons are important parts of the neurovascular unit. They have an essential role in adaptive vascular remodeling.

Myelin modulation might affect conduction. There is an emerging concept of myelin regulation as a new form of neural plasticity. Neuronal

activity regulates oligodendrocytes and myelinated axons. This will increase axon diameter and promote oligodendrocyte progenitor cell differentiation into oligodendrocytes and myelin sheath stabilization. This remodeling will occur days to weeks.⁹

Electrical activity promotes myelination. Action potentials and release of axonal factors make nearby oligodendrocyte processes begin ensheathment. Unmyelinated axons secrete neurotransmitters and neurotrophic factors extrasynaptically along axons. Electrical stimulation triggers local Ca^{2+} signaling in oligodendrocyte processes. This process will require synaptic vesicle exocytosis and glutamate receptors.²⁰ Synaptic vesicles can induce oligodendrocyte formation and myelination. Enhanced synaptic activity will result in an approximately 40% increase in myelination.²

MATERIALS AND METHODS

This review paper was based on journal reading. Keywords for literature searching were “myelin plasticity, nervous system, brain plasticity, research, astrocyte with filter in the last 10 years” in the PubMed website. The results showed 53 articles, consisting of 33 research articles and 20 review articles. Only research articles were included. Other articles in the references were added based on the previously selected journals.

RESULTS AND DISCUSSION

Intrinsic and adaptive myelination for smart wiring in the brain

Myelination has two phases, i.e. intrinsic and adaptive. These two phases generate “smart wiring” to make active axons become more myelinated. Myelination might play an important role

in learning through activity-dependent modification of an initially hardwired pattern. Adaptive myelination means myelin plasticity regulated by activity. There is an intrinsic pathway within oligodendrocytes. Oligodendrocyte precursor cells guide oligodendrocyte differentiation and axon myelination.²¹ Oligodendrocyte processes sense physical axon diameters to select axons. A longer axon will have a longer myelin sheath diameter. Therefore, an oligodendrocyte-intrinsic program establishes a pattern of myelination, and adaptation occurs to modify myelin sheath number and/or properties.^{8,12}

A transcriptional (intrinsic) program prior to differentiation will be held in the absence of molecular cues from axons. This program will yield the basal sheath number and/or size of the myelin sheath. The oligodendrocyte processes will respond locally to adapt the number and size of the myelin sheath based on extrinsic cues or activities. Decreasing the signal and/or extrinsic (adaptive) activity would result in a reduction in sheath size and/or number and conduction velocity.^{8,13}

Intrinsic myelination yields myelin sheaths of physiological length. There are two intrinsic mechanisms to instruct myelin sheath size. First, oligodendrocytes sense and respond to the physical size of axons. Second, oligodendrocyte populations exist with heterogeneous intrinsic programs.¹⁶

There is a strong correlation between axon diameter and myelination (including myelin sheath length and thickness). Oligodendrocytes can myelinate axons with diameters greater than 0.4 μm . In the corpus callosum, 80% of myelinated axons have a diameter > 0.4 μm . Initial ensheathment requires a minimal diameter of 0.3–0.4 μm .²²

The axon diameter can function as a signal that determines myelin sheath length. The ratio of axon diameter to the outer diameter of the myelin sheath

is approximately 0.7 μm . Internode length increases with axonal diameter. Oligodendrocytes have curvature-sensitive mechanisms to regulate the lateral expansion of myelin membranes along the axon. There is a linear correlation between axon diameter and internode length or thickness.¹⁶

Heterogeneous oligodendrocytes may determine myelin sheath length. Heterotopic and orthotopic transplantation of oligodendrocyte progenitors in gray or white cortical matter into the same or reciprocal region showed variable rates of oligodendrocyte proliferation and differentiation. Oligodendrocyte morphology differences revealed intrinsic differences in the sheath formation programs. Within the same physical and chemical environment, spinal cord oligodendrocytes generated longer sheath lengths than cortical oligodendrocytes. Therefore, both extrinsic environmental factors and intrinsic differences between oligodendrocyte populations determine myelin sheath length.^{16,23}

Adaptive myelination means adaptation of intrinsic myelin sheaths.²² Adaptive myelination has an important role in myelin plasticity.¹³ There will be changes in oligodendrocytes and the myelin they form. This occurs first as a response to activity-enhanced conduction, and active pathways will be reinforced accordingly. Myelin-forming oligodendrocytes are found in white and gray matter of the central nervous system (CNS). Rapid salutatory conduction is facilitated by the concentration of voltage-dependent sodium channels at the gap between sheaths, i.e., the nodes of Ranvier. The formation of newly differentiated oligodendrocyte cells improves motor learning.²⁴ Myelination in the cortex is reduced by social isolation and avoidance. Myelin formed by newly generated oligodendrocytes might alter axonal conduction velocities.¹⁵

Signal in myelination

Schwann cells sort larger axons and form the myelin sheath in the peripheral nervous system. Neural Wiskott–Aldrich syndrome protein (N-WASP) integrates extracellular signals to control actin and the cytoskeletal complex. In N-WASP-deficient nerves, Schwann cells are able to sort and ensheath axons; however, most of the cells cannot myelinate. Some of them form unusually short internodes or myelin misfolding. Therefore, N-WASP is very important for myelination. This protein is essential for spiral membrane wrapping and longitudinal extension of myelinating Schwann cells. N-WASP arranges myelination through actin modulatory function and regulation of endocytic vesicle trafficking.⁴

Axon has a selective mechanism. Axon activity is dependent on specific protein secretion. One of the secretions is vesicle-associated membrane protein (VAMP) family proteins, including synaptobrevin / VAMP2. Without secretion of VAMP proteins, oligodendrocyte membrane sheaths might be formed, but they will not be extended. These membranes will be retracted at a higher frequency. VAMP2-dependent secretion from axons promotes myelin sheath growth.¹³

Myelination *in vitro* is impaired by the actin polymerization inhibitor cytochalasin D and blocking myosin II activity. The small Rho GTPase family members Rac1, Cdc42, and Rho A are crucial in PNS myelination. GTPases regulate the assembly of filamentous actin. Rho/Rho kinase signaling promotes the coordinated movement of the myelin sheath. Rac1 is required for Schwann cell process extension. Cdc42 may be required for membrane wrapping. It is also important in promyelinating to myelinating Schwann cell transition.⁴

Activity-related signals that may adapt myelin are brain-derived neurotrophic factor (BDNF), platelet-

derived growth factor (PDGF), adenosine 5'-triphosphate (ATP), and glutamate.^{2,5,25-27} These molecules are able to increase oligodendrocyte progenitor cell (OPC) proliferation and/or differentiation. BDNF is secreted from cortical neurons after optogenetic stimulation.^{28,29} BDNF switches oligodendrocytes to a form of myelination dependent on NMDA (N-Methyl-D-aspartate) receptors.^{30,31} Without BDNF, there will be hypomyelination and a decrease in axon diameter. Akt (PKB/protein kinase B) and neuregulin (NRG) are important in regulating axon wrapping and myelin sheath thickness in the peripheral nervous system.¹⁶

Activating Akt or MAPK (mitogen-activated protein kinase) signaling in differentiated oligodendrocytes results in plasticity in the form of an increase in myelin thickness or the addition of extra myelin sheaths.¹³ Akt is activated initially along the internode. It is dependent on the NRG on the axon. Activated Akt is detected once compact myelin has formed.^{19,32}

Oligodendrocyte progenitor cells in the white matter will only proliferate in response to PDGF. This reveals that intrinsic mechanisms are crucial for the differential proliferative response of oligodendrocyte progenitor cells. The rate of oligodendrocyte progenitor cell division is greater in white matter than in gray matter.²

Epigenetic changes driven by social isolation during adulthood could influence the expression of members of the NRG1-ErbB pathway. NRG is important to switch oligodendrocytes from activity-independent to activity-dependent states. The condition will enhance myelination in response to glutamate release by neurons.^{2, 22, 32}

Formerly, neuroanatomists view myelin as a static structure, which is only modified through damage. However, recently, there has been a postulate connection between nervous

system function and plasticity with dynamic myelination. Myelination is easily observed using lipophilic stains. Myelin enhances neural circuit function and behavior, while functional activity increases myelination. Myelination is related to cognitive development, such as decision making, reading, and vocabulary. Myelination has occurred continually for decades. Therefore, dynamic myelination is affected by functional activity. It is an important part of learning. Neural circuit plasticity is closely related to myelination. The possibility of myelin plasticity was revealed when scientists observed white matter changes in the learning process. Action potential firing in axons can influence myelination.¹

Dynamic regulation of myelin as a novel form of brain plasticity

The dynamic remodeling of myelin continues throughout life. Dynamic myelin remodeling is a mechanism for myelin plasticity. It depends on oligodendrocyte progenitor cell numbers that differentiate into oligodendrocytes. Approximately 2.5% of new oligodendrocytes are added to the adult human cortex (gray matter) annually; however, only approximately 0.33% are added to the corpus callosum (white matter). Continuous myelin remodeling throughout the lifetime makes neural networks fine-tuned. It contributes to brain plasticity. Dynamic myelination is regulated by experience and environment. Training and learning will increase white matter myelination. Motor skill learning will enhance oligodendrocyte production.²

De novo myelination might take place at previously unmyelinated segments, replacing retracting or damaged myelin segments of pre-existing oligodendrocytes. Pre-existing oligodendrocytes might adjust the structural parameters of their myelin

sheath to modify nerve conduction velocity. Myelin remodeling is achieved by adding or removing myelin membrane layers.¹⁴

Myelin remodeling is a slower and secondary process that responds to the dynamics of neural networks. Learning makes an adjustment to myelination patterns to cope with the new needs of the neural network. It is also crucial for providing important homeostatic control. Remodeling of existing myelin sheaths and adjustment of the Ranvier node length will provide alternative and fast routes. Finally, myelin could adapt to neuronal activity changes either in a slow or fast way.^{8,14,32} Myelin thickness is regulated by changes in neuronal activity.³³

There is an active role for dynamic myelination in adult brain plasticity. Myelin plasticity might be evidence of which experience can shape brain structure and function. Myelin plasticity is important in information integration. Brain plasticity is associated with the concept of synaptic plasticity.¹⁴⁻¹⁶

Myelin plasticity is associated with learning and motor function. Myelin changes might affect the function of neural networks. It depends on neural signals. Dysregulation of myelin plasticity can deteriorate myelin microstructure. Aberrant circuit function might occur. Cell proliferation might also be damaged.³⁴

Connections between neurons and modifying the strength of synapses are a very important part of plasticity. Finally, the speed and time of information transmitted between relay points have profound effects. Spike-time arrival is crucial in neural coding, neuronal integration and synaptic plasticity. Thus, the most effective mechanism for reaching maximal conduction velocity is myelination. Conduction time is essential in synaptic plasticity. Proper conduction delay could be achieved by genetic instruction, myelinating unmyelinated

axons, or modulating the thickness of the myelin sheath. White matter abnormalities could make conduction delay suboptimal.¹

White matter structure can change after learning and functional experience, such as playing the piano, learning to read, mastering some skills, etc.^{15,18,35} Myelination might be affected by functional activity as a homeostatic response to neural activity or driven by learning. Increased myelination is found in learning complex motor tasks.¹⁶ Synaptic plasticity must be accompanied by myelination to regulate neural development from early life. Myelin plasticity is correlated with improved cognitive performance.¹

The main function of white matter tracts is rapid impulse conduction. It could be achieved by optimizing myelin sheath length and thickness. Gray matter is needed for more intricate connectivity. Therefore, there are greater variations and alterations in circuit function due to activity-dependent plasticity.^{16,19}

Genetic factors control about 75–90% of the variation in white and gray matter in the frontal and temporal lobes. Environmental changes regulate the corpus callosum white matter.^{2,26} Examples of environmental changes are unfamiliar foreign speech sounds, musical training, and extraneuronal changes such as increases in glial cell size and number, as well as angiogenesis.³⁶

Astrocyte role in myelination and plasticity

Active signaling between astrocytes and neurons is gliotransmission. It is important in brain function and signal integration. Astrocytes mainly signal through high-affinity slowly desensitizing receptors by means of gliotransmitters at the gap junction.³⁷ Oligodendrocytes are coupled to astrocytes (O: A coupling) through gap junctions. Gap junctions might serve as diffusion routes for ions

and small molecules. Gliotransmitters are important neuroactive substances for memory.³⁸

Gap junctions have special protein families, namely, connexin and pannexin. There are 21 different types of connexin. The most famous is Cx43.³⁸ Astrocytes perform local processing of synaptic information. Astrocytes are endogenous regulators of basal transmission at central synapses. Peripheral and central nervous tissue damage will activate astrocytes. Astrocytes are able to detect synaptic events at special subcellular functional sites called astrocytic

compartments.³⁹

Astrocytes are important for synaptic genesis and plasticity, including the formation and stabilization of synaptic connections during brain development.⁶ Astrocytes integrate and adapt to synaptic strength according to the synapse history. It may vary according to long-term changes. Thus, astrocytes undergo synaptic plasticity changes.⁴⁰ Astrocytes have an important role as synaptic network integrators.³⁹ Decreasing astrocyte number will cause loss of presynaptic plasticity.⁶

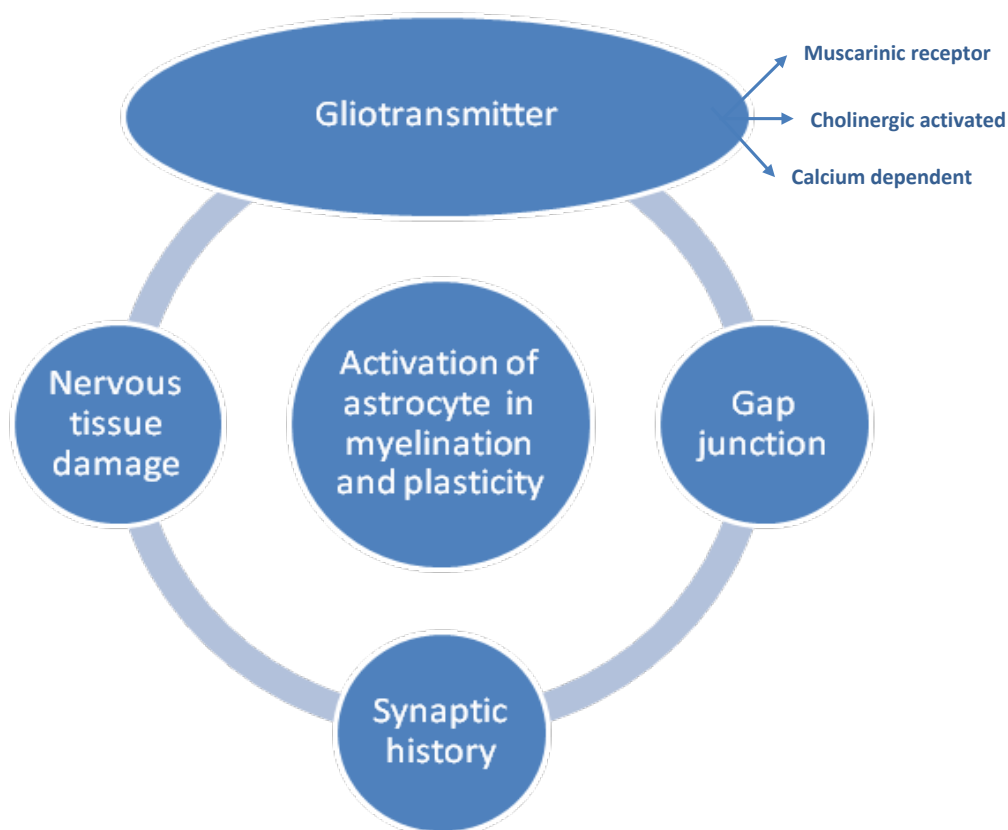


FIGURE 2. The factors that affect astrocyte role in myelination and plasticity

The role of astrocytes in myelination and plasticity depends on some factors. Gliotransmission, gap junctions, nervous tissue damage, and synaptic history were observed (FIGURE 2). In addition to these important factors, there are some receptors that have important roles in helping gliotransmitters during the

myelination process. These receptors are muscarinic, cholinergic, and calcium dependent release.⁴¹⁻⁴³

Chen *et al.*⁴¹ found that astrocytes might mediate cortical plasticity in the nucleus basalis by cholinergic modulation via muscarinic receptors. Potentiation in neurons might occur due to an astrocytic

calcium-driven mechanism. Takata *et al.*⁴² and Navarrete *et al.*⁴³ reported that cholinergic-activated astrocytes can induce synaptic plasticity. Navarrete *et al.*⁴³ found that sensory or electrical stimulation of the septal nucleus will increase calcium concentration in hippocampal astrocytes. Astrocyte Ca²⁺ signaling is essential in cholinergic-induced synaptic plasticity and long-term potentiation. This will affect the cellular basis of brain storage information in learning and memory.⁴²

Astrocytes can induce a plasticity cascade in synapses and alter orientation-specific responses potentially through astrocytic calcium-dependent release of gliotransmitters.⁴¹ Sibille *et al.*⁴⁴ found that astrocytes were important in short-term plasticity. Astrocytes play a critical role in adjusting synaptic efficacy.

CONCLUSION

Myelination changes in response to activity were known nearly a century ago. Myelin plasticity might occur throughout the lifetime. Dynamic myelin plasticity might reveal that experience shapes the brain resembles synaptogenesis. In the beginning, it is a hard-wired process that is affected by the experience. This smart wiring has an essential role in learning. Myelin determines the critical period for learning and developing neural circuits. Dynamic regulation of myelination might refine neuronal circuit function. Further studies are needed to consider myelinated axons as functional units. There should be in-depth studies about astrocytes, gliotransmitters, and gap junctions.

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